Two Decades of Universal Hepatitis B Vaccination in Taiwan: Impact and Implication for Future Strategies


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Background & Aims: Following the world’s first successful implementation of a universal hepatitis B virus (HBV) vaccination program for infants in Taiwan 20 years ago, we performed this study to evaluate the long-term protection afforded by HBV vaccination and to rationalize further prevention strategies.

Methods: HBV seromarkers, including hepatitis B surface antigen (HBsAg) and antibodies to HBsAg (anti-HBs) and core antigen (anti-HBc), were studied in 18,779 subjects from neonates to adults below 30 years of age in 2004. The birth cohort effect was evaluated by comparing the results of the same birth cohorts at different ages among this survey and the previous 1984, 1989, 1994, and 1999 surveys.

Results: The seropositive rates for HBsAg, anti-HBs, and anti-HBc were 1.2%, 50.5%, and 3.7%, respectively, in those born after the vaccination program (<20 years of age) in 2004. A positive maternal HBsAg status was found in 89% of the HBsAg seropositive subjects born after the vaccination program. The absence of an increase in HBsAg seropositive subjects at different ages in the same birth cohorts born after the vaccination program implied no increased risk of persistent HBV infection with aging.

Conclusions: Universal HBV vaccination provides long-term protection up to 20 years, and a universal booster is not indicated for the primary HBV vaccinees before adulthood. Maternal transmission is the primary reason for vaccine failure and is the challenge that needs to be addressed in future vaccination programs. This may include an appropriate hepatitis B immunoglobulin administration strategy for high-risk infants and involve efforts to minimize noncompliance.

Hepatitis B virus (HBV) infection is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in many parts of the world. The majority of chronic HBV carriers became infected early in life while living in endemic areas, especially before the age of 2 years. As many as 15% of healthy adults in Taiwan are chronic hepatitis B surface antigen (HBsAg) carriers. The world’s earliest nationwide universal vaccination program aimed at early prevention was launched in Taiwan in July 1984. This program reduced not only the rate of persistent infection and the total prevalence of HBV in the younger generation but also the occurrence of childhood hepatocellular carcinoma and fulminant hepatitis in Taiwan.

We conducted a series of prospective seroepidemiologic surveys in Taipei City to monitor the efficacy of the vaccination program. The first survey was performed just before the mass vaccination program in 1984, followed by similar surveys in 1989, 1994, and 1999. Adequate protection against HBV for 14 years following universal HBV vaccination in infancy was reported in another longitudinal follow-up study. However, waning immunity to HBV and the need for a booster dose, particularly when the primarily vaccinated children become sexually active adolescents and thereby experience an increased risk of parenteral exposure, remain debatable. The best way to confirm long-term protection is to observe any increase in persistent infection, surrogated by the HBsAg seropositive rate in adolescents from an HBV endemic area.

Effective vaccination and extensive coverage of the vaccinees are critical in achieving effective HBV infection control. Taking Taiwan as an example of an HBV endemic area, this study aimed to evaluate the long-term protection and any emerging threat of infection 2 decades after the initiation of a mass HBV vaccination program. The study also intended to shed light on future strategies in HBV control. In addition, we also explored the possible causes of persistent HBV infection in the birth cohorts born in the vaccination era.

Materials and Methods

Vaccination Program

The HBV universal vaccination program was launched in Taiwan on July 1, 1984. The vaccination covered newborns of HBsAg-carrier mothers from July 1984 to June 1986; the program was extended to all...
newborns since July 1986 and extended again to preschool children from July 1987 to June 1988. It was further extended to cover school children, teenagers, and then adults from 1988 to 1990.

Since 1991, the vaccination records of first-grade school children have been checked, and those children who were unvaccinated or incompletely vaccinated were given a catch-up HBV vaccination. Before July 1992, 4 doses of plasma-derived vaccine (Hevac B; Pasteur-Mérieux, Lyon, France; or its equivalent derivative, Lifeguard hepatitis B vaccine; Hsin-Chu, Taiwan) were given at 0, 1, 2, and 12 months of age. After July 1992, 3 doses of recombinant vaccine H-B-Vax II (5 µg/0.5 mL; Merck Sharp & Dohme, Rahway, NJ) or Engerix-B (20 µg/1 mL; SmithKline Beecham, Rixensart, Belgium) were administered at <1 week, 1 month, and 6 months of age.

In addition, all pregnant women were screened for HBsAg and hepatitis B e antigen (HBeAg) if HBsAg was positive. Hepatitis B immunoglobulin (HBIG) 0.5 mL (100 IU) was given within 24 hours after birth for newborns of HBeAg-positive or high titer of HBsAg (reciprocal titer >1:2560 by reverse passive hemagglutination test) carrier mothers.

Details of the vaccination program were described previously. The vaccination coverage rate was defined as the percentage of children receiving 3 or more doses of HBV vaccine. The immunization history was checked by examining the vaccination card and taking the history from the parents. Those who lost their vaccination cards or had unverified immunization histories were listed as unknown.

Study Population

From January to December 2004, serum samples were collected from 18,779 subjects as follows: 17,637 apparently healthy individuals (M/F, 9785:7832) younger than 20 years, who were born after the launch of the universal vaccination program, and 1142 individuals (M/F, 693:449) aged between 20 and 30 years. All of the subjects were recruited through routine health checks, poster advertisements, or health staff introductions. The overall recruitment rate was 82% for preschools, primary schools, and junior high schools (below the ninth grade). For high schools and university undergraduate and graduate students, the recruitment rate was 57% and 37%, respectively. The enrolled children’s parents or the subjects themselves signed an informed consent and provided the vaccination history, which was recorded in a health booklet distributed to each newborn by the Department of Health, if available. Because the program was not applied to all newborns until 1986, only the vaccination histories of those below 18 years (born after 1986) were included in the inquiries.

HBV Serology

Serum HBsAg and its antibody (anti-HBs) and antibody to hepatitis B core antibody (anti-HBc) were tested in all of the subjects. HBeAg and its antibody (anti-HBe) were tested if the serum sample was positive for HBsAg. All of the HBV serologic markers were performed by enzyme immunoassay (Abbott Laboratories, North Chicago, IL). Anti-HBs was considered positive if the titer was ≥10 mIU/mL. Maternal HBsAg status, which is routinely screened in pregnant women in Taiwan, was also investigated.

Statistical Analysis

Differences in frequency between groups were examined by χ² test with Yates correction or Fisher exact test, wherever appropriate. A P value of <.05 was considered statistically significant.

Results

Vaccine Coverage

The vaccination coverage rate was high in the population of subjects in this study. Infants (<1 year of age) had a high incomplete vaccination rate because 45% (50/110) were too young to complete the schedule. The incomplete vaccination rate (defined as the percentage of persons who received <3 doses of hepatitis B vaccines divided by the number of persons with clear vaccine histories) was approximately 5% except for toddlers (1–2 years of age), which was 0% (Table 1). Because the rate of unverified vaccine histories among high school and college students was high (Table 1), it is likely that incomplete coverage rates were underestimated in this age group. The vaccine coverage rate from the database of Taiwan’s Center of Disease Control is listed in Table 1.

Universal Vaccination Program Minimizes HBsAg Prevalence

HBsAg prevalence in this and 4 previous seroepidemiologic surveys in the same region showed a clear vaccination effect: those who were born after the implementation of the universal HBV vaccination program
had a lower seropositive rate compared with those born before the implementation (Figure 1). The prevalence rate of HBsAg in children <15 years of age was 0.5% (38/7234), which was lower than that of children aged 15–19 years (1.7%, 181/10,403) ($P < .0001, \chi^2$ test) and much lower than that of those >20 years of age, who were born before the universal vaccination program (124/1142, 10.9%) ($P < .0001, \chi^2$ test) (Table 2).

The HBsAg seropositive rates of each birth cohort did not increase with age, even in those who reached the age of 15–19 years. Table 3 lists the HBsAg seropositive rates of each birth cohort born after the vaccination program, at different ages, with the 4 sequential surveys conducted in 1989, 1994, 1999, and 2004. We did not include the birth cohort of those born from 1984 to 1986 because only high-risk neonates received an HBV vaccination during that period. A trend of stable or even decreased HBsAg positivity could be observed 17 years after their birth. The HBsAg positivity could be observed 17 years after their birth. The incomplete rate was calculated as the percentage of persons who received <3 doses of hepatitis B vaccines divided by the number of persons with clear vaccine histories. The high incomplete vaccination rate in infancy was due to those <6 months of age.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Age-specific hepatitis B surface antigen seropositive rates in the years of 1984, 1989, 1994, 1999, and 2004 in Taipei, Taiwan. In 1984, none of the subjects were under the universal vaccination coverage. In 1989, only children below 5 years of age were covered. Subsequently, children below 10, 15, and 20 years of age were covered by the universal vaccination in 1994, 1999, and 2004, respectively. Those who were born before the implementation of this program had a higher HBsAg carrier rate than those born after the implementation. The dotted line for 1984 represents the data before universal vaccination implementation, whereas the solid lines for 1989, 1994, 1999, and 2004 represent the data after the program.

<table>
<thead>
<tr>
<th>Birth cohort Age, y</th>
<th>No. of persons</th>
<th>No. unverified history</th>
<th>&lt;3 Doses</th>
<th>≥3 Doses</th>
<th>Incomplete rate, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Coverage rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–2004 &lt;1</td>
<td>110</td>
<td>0</td>
<td>50</td>
<td>60</td>
<td>45.5</td>
<td>—</td>
</tr>
<tr>
<td>2001–2003 1–2</td>
<td>235</td>
<td>8</td>
<td>0</td>
<td>227</td>
<td>0</td>
<td>96.6–98.0</td>
</tr>
<tr>
<td>1999–2001 3–4</td>
<td>709</td>
<td>49</td>
<td>37</td>
<td>623</td>
<td>5.6</td>
<td>93.6–98.0</td>
</tr>
<tr>
<td>1997–1999 5–6</td>
<td>993</td>
<td>76</td>
<td>45</td>
<td>872</td>
<td>4.9</td>
<td>91.8–93.4</td>
</tr>
<tr>
<td>1995–1997 7–8</td>
<td>651</td>
<td>127</td>
<td>31</td>
<td>493</td>
<td>5.9</td>
<td>93.2–93.5</td>
</tr>
<tr>
<td>1993–1995 9–10</td>
<td>681</td>
<td>145</td>
<td>45</td>
<td>492</td>
<td>8.4</td>
<td>91.1–92.1</td>
</tr>
<tr>
<td>1991–1993 11–12</td>
<td>1088</td>
<td>315</td>
<td>59</td>
<td>714</td>
<td>7.6</td>
<td>93.4–94.4</td>
</tr>
<tr>
<td>1989–1991 13–14</td>
<td>2767</td>
<td>875</td>
<td>147</td>
<td>1745</td>
<td>7.8</td>
<td>94.7–95.1</td>
</tr>
<tr>
<td>1986–1989 15–17</td>
<td>6531</td>
<td>3536</td>
<td>521</td>
<td>2474</td>
<td>17.4</td>
<td>86.9–89.7</td>
</tr>
</tbody>
</table>

**Table 1.** History and Coverage Rate of Hepatitis B Vaccination in Children and Adolescents in Taipei, Taiwan, 2004

NOTE. The sum of the persons receiving <3 doses and persons receiving ≥3 doses may not equal the number of study subjects. The discrepancies are due to those who lost their vaccination record booklets and had vaccine histories that could not be verified. Data are from the Center for Disease Control, Department of Health, Taiwan.

<sup>a</sup>The incomplete rate was calculated as the percentage of persons who received <3 doses of hepatitis B vaccines divided by the number of persons with clear vaccine histories. The high incomplete vaccination rate in infancy was due to those <6 months of age.
HBeAg/Anti-HBe Status of the Vaccine Failure Cases

We further studied the HBeAg/anti-HBe status of the 136 HBsAg seropositive children born after the implementation of the universal vaccination program, except for 5 cases without sufficient serum samples. The overall anti-HBe seropositive rate in this population was 29.0% (Table 4). The youngest who underwent HBeAg seroconversion was 11 years old.

No Increase in Natural Infection by Stable Anti-HBe Seropositivity

In the 2004 survey, the seroprevalence of anti-HBc was low (1.0%) in children under 15 years of age (Table 2). We excluded the infants who were under 1 year old because their anti-HBc was likely to be transplacental from their mothers. As the children aged, the anti-HBc seropositive rates increased to 4.0% in the 15- to 17-year-old and to 6.8% in the 18- to 19-year-old groups. The anti-HBc seropositive rate in the population born before universal vaccination was as high as 44% in this study.

Discussion

A high coverage rate of HBV vaccination is crucial in decreasing the prevalence of HBV infection. To evaluate whether the increase of anti-HBc with age in the 2004 survey was an actual increase in infection or a birth cohort effect, we took the cohort born during 1989–1993. Their anti-HBc seropositive rate was 2.7% (17/631) in 1994 and 1.9% (88/4536) in 2004 (χ² test, P < .005). The anti-HBc seropositive rates of this cohort did not increase with age.

The overall prevalence rate of anti-HBs was 50.3% in 2004. The highest anti-HBs prevalence rate was observed in those younger than 5 years of age (Table 2). The anti-HBs seropositive rate decreased to 50% in the school children and 37% in the 15- to 17-year-old group, which was the first generation covered by the universal vaccination program.

Table 2. HBV Seroprevalence Rate (%) After 2 Decades of Universal Vaccination in Taipei, Taiwan, 2004

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. persons</th>
<th>HBsAg⁺ (95% CI)</th>
<th>Anti-HBc alone (95% CI)</th>
<th>Anti-HBc⁺ Anti-HBs (95% CI)</th>
<th>Anti-HBs alone (95% CI)</th>
<th>Negative (95% CI)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>110</td>
<td>0.9 (0.7–1.1)</td>
<td>6.4 (5.9–6.8)</td>
<td>17.3 (16.6–18.0)</td>
<td>62.7 (61.9–63.6)</td>
<td>12.7 (12.1–13.3)</td>
</tr>
<tr>
<td>1–2</td>
<td>235</td>
<td>0.4 (0.4–0.5)</td>
<td>0</td>
<td>3.4 (3.3–3.6)</td>
<td>88.9 (88.7–89.2)</td>
<td>6.4 (6.2–6.6)</td>
</tr>
<tr>
<td>3–4</td>
<td>709</td>
<td>0.4 (0.4–0.4)</td>
<td>0</td>
<td>0.1 (0.1–0.2)</td>
<td>80.8 (80.7–80.9)</td>
<td>15.8 (15.7–15.9)</td>
</tr>
<tr>
<td>5–6</td>
<td>993</td>
<td>0.5 (0.5–0.5)</td>
<td>0</td>
<td>0.5 (0.5–0.5)</td>
<td>52.3 (52.1–52.4)</td>
<td>43.3 (43.2–43.4)</td>
</tr>
<tr>
<td>7–8</td>
<td>651</td>
<td>0.6 (0.6–0.6)</td>
<td>0.1 (0.1–0.2)</td>
<td>0.5 (0.4–0.5)</td>
<td>49.5 (49.3–49.6)</td>
<td>49.0 (48.9–49.1)</td>
</tr>
<tr>
<td>9–10</td>
<td>681</td>
<td>0.3 (0.3–0.3)</td>
<td>0.1 (0.1–0.2)</td>
<td>1.5 (1.4–1.5)</td>
<td>43.3 (43.2–43.5)</td>
<td>55.1 (55.0–55.2)</td>
</tr>
<tr>
<td>11–12</td>
<td>1088</td>
<td>0.5 (0.5–0.5)</td>
<td>0.2 (0.2–0.2)</td>
<td>0.5 (0.5–0.6)</td>
<td>41.7 (41.6–41.8)</td>
<td>57.0 (56.9–57.1)</td>
</tr>
<tr>
<td>13–14</td>
<td>2767</td>
<td>0.6 (0.6–0.6)</td>
<td>0.5 (0.5–0.5)</td>
<td>1.2 (1.2–1.2)</td>
<td>41.8 (41.8–41.9)</td>
<td>55.0 (55.0–55.1)</td>
</tr>
<tr>
<td>15–17</td>
<td>6531</td>
<td>1.5 (1.5–1.5)</td>
<td>0.5 (0.5–0.5)</td>
<td>2.1 (2.1–2.1)</td>
<td>34.9 (34.9–34.9)</td>
<td>62.6 (62.6–62.6)</td>
</tr>
<tr>
<td>18–19</td>
<td>3872</td>
<td>2.1 (2.1–2.1)</td>
<td>0.3 (0.3–0.3)</td>
<td>4.0 (3.9–4.0)</td>
<td>68.5 (68.5–68.5)</td>
<td>26.2 (26.2–26.2)</td>
</tr>
<tr>
<td>Total</td>
<td>17,637</td>
<td>1.2</td>
<td>0.4</td>
<td>2.1</td>
<td>48.4</td>
<td>48.0</td>
</tr>
</tbody>
</table>

Cl, confidence interval.

*All HBsAg-positive subjects had positive anti-HBc except in 13 cases with positive HBsAg and negative anti-HBc.

The negative rate represents those who were negative for all 3 HBV seromarkers: HBsAg, anti-HBc, and anti-HBs.

Table 3. HBsAg Seropositive Subjects According to Birth Cohorts Born After the Vaccination Program

<table>
<thead>
<tr>
<th>Birth year</th>
<th>Subjects</th>
<th>Positivity (%)</th>
<th>OR (95% CI)</th>
<th>Subjects</th>
<th>Positivity (%)</th>
<th>OR (95% CI)</th>
<th>Subjects</th>
<th>Positivity (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987–1988</td>
<td>205</td>
<td>3 (1.46)</td>
<td>1</td>
<td>371</td>
<td>3 (0.81)</td>
<td>1</td>
<td>662</td>
<td>1 (0.15)</td>
<td>1</td>
</tr>
<tr>
<td>1989–1993</td>
<td>574</td>
<td>2 (0.35)</td>
<td>0.23 (0.04–142)</td>
<td>455</td>
<td>7 (1.54)</td>
<td>1.92 (0.49–4.46)</td>
<td>4190</td>
<td>25 (0.60)</td>
<td>3.97 (0.53–29.37)</td>
</tr>
<tr>
<td>1994–1998</td>
<td>241</td>
<td>1 (0.41)</td>
<td>0.28 (0.03–2.71)</td>
<td>1990</td>
<td>10 (0.50)</td>
<td>0.62 (0.17–2.26)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1999–2003</td>
<td>1054</td>
<td>5 (0.47)</td>
<td>0.32 (0.08–1.35)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Trend test χ² = .35, P = .16

cohort. Moreover, to ensure a high coverage rate, the government requests students to present their vaccination records when they enter primary school.\textsuperscript{19} If they do not complete the vaccinations, it is mandatory to receive a catch-up vaccine.

Compared with children $<$15 years of age, those $>$15 years of age had a higher HBSAg seropositive rate of 1.5%. The anti-HBc-positive rate was 4.0% for the 15- to 17-year-old group (1986–1988 birth cohort), whereas the HBSAg seropositive rate and the anti-HBc-positive rate were 2.1% and 6.8%, respectively, for the 18- to 19-year-old group (1984–1986 birth cohort) in the 2004 survey (Table 2). The data suggest a possibility of increased virus contact in that period.

The relatively higher seropositive rates of HBSAg and anti-HBc in the 15- to 17-year-old group (1986–1988 birth cohort) are better explained by the lower coverage rates of HBV vaccination, ie, 86.9%–89.7% in the national birth cohort) are better explained by the lower coverage rates of HBV vaccination, ie, 86.9%–89.7% in the national birth cohort (1984–1986 birth cohort) in the 2004 survey (Table 2). The data suggest a possibility of increased virus contact in that period.

The results of birth cohort analysis (Table 3) in this study clearly showed no increase of the seropositive rates of HBSAg and anti-HBc when the vaccinees progressed to 17 years of age. These data validated the proposition that the risk of becoming a chronic carrier through sexual contact should be minimal. Furthermore, previous studies demonstrated that the risk of becoming a chronic carrier after HBV infection decreased dramatically with age: 25% in preschool children and 2.7% in university students.\textsuperscript{3,20} All of the above data suggest that a universal booster vaccine might not be necessary after primary vaccination.

Our previous long-term prospective study also demonstrated very low new seroconversion rates to positive anti-HBc in vaccinees who lost their anti-HBs and were hyporesponsive or nonresponsive to a booster dose of vaccine.\textsuperscript{15,21} These findings are compatible with 2 other long-term follow-up studies of vaccinated native Alaskans, in which the cohorts showed waning anti-HBs but no clinical HBV infection.\textsuperscript{22,23}

Infants with a positive family history of HBV infection, especially those born to HBSAg-positive mothers, are the high-risk group for immunoprophylaxis failure. The problem that remains is how to overcome these failures in the universal vaccination era. The high-risk group may be the babies born to HBSAg-positive mothers with a high viral load.\textsuperscript{24,25} Several strategies have been proposed to block mother-to-infant transmission, and each has its pros and cons (Table 5). Our current program is to administer HBIG only to newborns born to HBSAg-positive mothers because the infection rate in infants born to HBSAg-negative, HBSAg-positive mothers is low. In the future, we may screen pregnant mothers for HBSAg, and administer HBIG to all newborns born to HBSAg-positive mothers within $<$12 hours of birth in addition to the complete 3-dose HBV vaccines.\textsuperscript{26} In the meantime, a prospective, randomized trial would be helpful to justify the cost-effectiveness of screening the HBeAg or HBV DNA statuses of pregnant mothers and administering HBIG only to babies born to HBSAg-positive or high-serum HBV DNA mothers. Such an approach targets the high-risk group and may save on the cost of administering HBIG to infants of low viremic carrier mothers, although it will involve the cost of HBeAg or HBV DNA screening for pregnant mothers. For countries or regions with very limited resources, the minimal requirement is to give a complete 3-dose universal vaccination to infants.

Other possible causes of mother-to-infant transmission in vaccine failure subjects include intrauterine HBV infection,\textsuperscript{27} vaccine escape variants,\textsuperscript{28,29} and hyporesponsiveness or nonresponsiveness to the vaccine. Hypo- and nonresponsive HLA types have been associated with certain HLA types.\textsuperscript{30,31} Three supplemental doses of recombinant HBV vaccines were shown to be effective in eliciting a good immune response in primary infant or toddler hyporesponders.\textsuperscript{32} New vaccines, including those containing PreS1 and PreS2 antigens, may help to overcome this problem.\textsuperscript{33} A high coverage rate can rule out noncompliance as the reason for new HBSAg carriage in Taiwan, particularly

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**Table 4.** Hepatitis B e Antigen and Antibody Status of the HBSAg Carriers’ Children Born After the Universal Vaccination

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>No. of tested carriers</th>
<th>No. of HBeAg(+) (%)</th>
<th>No. of anti-HBe(+) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>5</td>
<td>5 (100)</td>
<td>0</td>
</tr>
<tr>
<td>5–9</td>
<td>8</td>
<td>8 (100)</td>
<td>0</td>
</tr>
<tr>
<td>10–14\textsuperscript{a}</td>
<td>23</td>
<td>15 (65.2)</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>15–17\textsuperscript{a}</td>
<td>95</td>
<td>54 (56.8)</td>
<td>31 (32.6)</td>
</tr>
<tr>
<td>Total\textsuperscript{a}</td>
<td>131</td>
<td>82 (62.6)</td>
<td>38 (29.0)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Three patients were seropositive for both HBeAg and anti-HBe in the 15- to 17-year-old age group; 1 and 7 patients were seronegative for both markers in the 10- to 14- and 15- to 17-year-old age groups, respectively.
after 1990. Very few horizontal infections, as shown in our subjects with negative maternal HBsAg, still exist even under the universal vaccination program.

We estimated that more than 30% of HBsAg carrier children would undergo spontaneous HBeAg seroconversion before adulthood in this study (Table 4). This event was barely seen before the age of 10 years but started to occur during adolescence. A long-term follow-up will help to elucidate the prognostic relevance of HBeAg seroconversion during childhood.

A universal booster dose is not necessary up to 20 years after the primary vaccination because HBsAg and anti-HBc seropositivity do not increase. This study also revealed that maternal transmission is the primary reason for vaccine failure and the main problem to be resolved. Our previous study demonstrated that 97% of hepatocellular carcinoma children were HBsAg-positive and >90% of hepatocellular carcinoma patients had an HBsAg-positive mother. However, 42%–57% of pediatric hepatocellular carcinoma patients did not receive HBIG at birth.10

Promoting HBIG coverage rates in infants born to HBsAg carrier mothers is certainly one important way to block mother-to-infant transmission. Although this is somewhat less necessary after the vaccination era, the methods for the prevention of horizontal transmission, such as blood bank screening, avoidance of skin tattooing, use of disposable needles, and condom use in sexual contact, still need continuous implementation.34

Until 2003, 151 of 192 (79%) World Health Organization member states had integrated universal infant or childhood hepatitis B vaccination into their expanded programs of immunization.35 Attaining global immunization coverage is a goal that is still unmet. Nevertheless, we anticipate that HBV infection will be controlled to a large extent along with HBV-related liver diseases.

In conclusion, this study demonstrated the tremendous impact of a mass vaccination program on HBV infection. Universal HBV vaccination in infancy can provide effective long-term protection. Moreover, we found that it reduces not only the persistent infection rate but also the total infection rate of HBV and that a universal booster for adolescents was not indicated. Mother-to-infant transmission remains the key cause of vaccine failure that needs to be overcome. For a better prevention of HBV infection in the future, the identification of subjects at a high risk for mother-to-infant transmission and effective strategies to block this transmission are mandatory.

### Table 5. Pros and Cons of 3 Different Strategies for Hepatitis B Immunoglobulin Administration to Newborns

<table>
<thead>
<tr>
<th>Screening methods for mothers</th>
<th>Immunization for babies</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg only</td>
<td>Vaccines for all NBs,*</td>
<td>One simple and inexpensive blood test for mothers; proven efficacy</td>
<td>Relatively expensive because of increased HBIG use</td>
</tr>
<tr>
<td></td>
<td>HBIG for NBs born to HbsAg-positive mothers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg; if positive, then HBeAg</td>
<td>Vaccines for all NBs, HBIG for NBs born to HBeAg-positive mothers</td>
<td>Two easy tests for mothers; proven efficacy; will save on the cost of HBIG for NBs born to HBeAg-negative mothers</td>
<td>Some HBeAg-negative mothers still have a high viral load, and their babies may be susceptible to HBV infection</td>
</tr>
<tr>
<td>HBsAg; if positive, then HBV DNA</td>
<td>Vaccines for all NBs, HBIG for NBs born to mothers with high serum HBV DNA</td>
<td>Theoretically appropriate, targets the NBs in most need (those with a high maternal viral load)</td>
<td>Expensive screening test; no consensus on “high-risk” maternal serum DNA cut-off level; no proven efficacy</td>
</tr>
</tbody>
</table>

NB, newborn.

### References


